UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/672,126	09/27/2000	Gunther Hartmann	C1039/7044 (AWS)	6887

7590 03/24/2004

Alan W Steele
c/o Wolf Greenfield & Sacks PC
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2211

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/672,126	HARTMANN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,47,65,82,103,122,143,159,176,199 and 201-280* is/are pending in the application.

4a) Of the above claim(s) *47,122,143 and 159* is/are withdrawn from consideration.

5)☒ Claim(s) *1-24,65,82,103 and 202-263* is/are allowed.

6)☒ Claim(s) *176,199 and 264-280* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/15/03, 12/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on 12/29/03 have been entered.

Claims 1-24, 47, 65, 82, 103, 122, 143, 159, 176, 199 and 201-280 are pending in the present application. Claims 47, 122, 143 and 159 are withdrawn from further consideration because they are drawn to non-elected inventions.

Accordingly, claims 1-24, 65, 82, 103, 176, 199, 202-280 are examined on the merits herein.

Response to Amendments

The rejection under 112 U.S.C., first paragraph, is withdrawn in light of Applicants' amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 176, 199, and 264-278 are rejected under 35 U.S.C. 102(b) as being anticipated by Krieg et al. (WO 9602555; IDS). **This is a new ground of rejection.**

Claim 176 and its dependent claims are directed to a method of stimulating production of a plurality of type I interferon (IFN) subtypes, comprising contacting (both *in vitro* and *in vivo*) type I interferon producing cells (IPCs) with an amount of

immunostimulatory nucleic acid effective to induce secretion of at least two type I interferons, wherein said immunostimulatory nucleic acid is at least 10 nucleotides long and comprises a poly-G sequence at each end and a central palindromic sequence comprising an unmethylated CpG dinucleotide.

Claim 199 is drawn to a method of inhibiting IL-12 production, comprising contacting IL-12-producing cells, in the presence of interferon-producing cells under conditions in which the IL-12-producing cells normally produce IL-12, with an immunostimulatory nucleic acid effective to induce secretion of at least two type I interferons, wherein said immunostimulatory nucleic acid is at least 10 nucleotides long and comprises a poly-G sequence at each end and a central palindromic sequence comprising an unmethylated CpG dinucleotide.

Examiner notes that only the term "**natural interferon-producing cell**" refers to a specialized type of leukocyte that is the chief producer of IFN-alpha in response to enveloped viruses, bacteria, and tumors (see page 49, lines 17-19), and not the terms "type I interferon producing cells" or "interferon-producing cells" as recited by the instant claims.

Krieg et al. teach a composition comprising an immunostimulatory oligonucleotide that contains a consensus mitogenic CpG motif represented by the formula: 5'-$X_1X_2CGX_3X_4$-3', wherein C and G are unmethylated, X_1, X_2, X_3 and X_4 are nucleotides, preferably the immunostimulatory oligonucleotides are between 2 to 100 base pairs or between 8 to 40 in size and methods of using the same (page 7, see Summary of the Invention). Krieg et al. teach that an oligonucleotide comprises multiple

nucleotides linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., C, T, U) or a substituted purine (e.g., A or G) and that they can be obtained from existing nucleic acid sources or they can be synthesized (page 9, lines 16-25). Krieg et al. also teach that for *in vivo* use, oligonucleotides can be stabilized via phosphate backbone modifications (e.g., phosphorothioate modified backbone) (page 9, lines 27-35). Krieg et al. further disclose that the most stimulatory sequence identified was 5'-TCAACGTT-3' which contains the self complementary "palindrome" AACGTT, and that an immunostimulatory oligonucleotide containing Gs at both ends showed increased stimulation, particularly if the ODN were rendered nuclease resistant by phosphorothioate modification of the terminal internucleotide linkages, with an exemplified ODN 1585 having the sequence 5'-GGGGTCAACGTTCAGGGGGG-3' (page 13, lines 19-30).

Krieg et al. also teach an *in vivo* method for enhancing an immune response in a mammalian subject by administering to the subject the composition disclosed above or contacting the composition with lymphocytes (e.g., B cells or NK cells) obtained from the subject ex vivo and the activated lymphocytes are then re-implanted into the subject (page 21, lines 10-26, page 22, line 9 continues to line 25 of page 24). Krieg et al. also teach a method of contacting human peripheral blood monocytes (PBMCs) with the CpG ODNs in culture to test their mitogenic effects on human cells and peripheral blood monocyte cells (page 25, lines 28-31). Please note that a mammalian subject has type I interferon producing cells (e.g., B-cells, pDC2s) and IL-12-producing cells; human

peripheral blood monocyte cells contain a rare CD4+/MHC class II+ cell population and that B cells are also known to be type I interferon producing cells.

Since the methods taught by Krieg et al. are indistinguishable from those of the presently claimed invention (same starting materials and same method steps), it is inherent that the methods taught by Krieg et al. also produce the same effects as recited by the instantly claimed methods.

Therefore, Krieg et al. anticipate the instant claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 176, 199, 264, 266, 268-280 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 6, 11-13, 16 and 18 of copending Application No. 10/017,995. Although the conflicting claims are not identical, they are not patentably distinct from each other because a method of inhibiting angiogenesis in a subject in need of such treatment

comprising administering to the subject at least one anti-angiogenic nucleic acid molecule comprising at least SEQ ID NOs:1-1093 in the copending Application has the same steps and same starting materials (Anti-angiogenic nucleic acids of SEQ ID NOs: 997, 988, 990, 995, 979, 974, 1049, 1072, 1077 and 1079 have the same sequences as SEQ ID NOs: 7, 9, 11, 13, 24, 25, 30, 33, 36 and 37, respectively, of the presently claimed invention) as the presently claimed methods. The co-pending Application specifically discloses that nucleic acid stabilization can be accomplished via backbone modifications, and one type of modified backbone is a phosphate backbone modification. For example, antiangiogenic nucleic acids including at least two phosphorothioate linkages at the 5' end of the oligonucleotide and multiple phosphorothioate linkages at the 3' end, preferably 5 or more, can in some circumstances protect the nucleic acid from degradation by intracellular exo- and endo-nucleases and thereby provide maximal activity (page 40, lines 25-33). As the mammalian subject treated in the method of the co-pending application has type I interferon producing cells and IL-12-producing cells, the administered anti-angiogneic nucleic acids of SEQ ID NOs: 997, 988, 990, 995, 979, 974, 1049, 1072, 1077 and 1079 would also be in contact with these cell populations. Therefore, the method of inhibiting angiogenesis in a subject in the co-pending application would inherently produce the same effects as the methods as claimed by the presently claimed invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 176 and 265-278 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,429,199 in view of Siegel et al. (Science 184:1835-1837, 1999). **This is a new ground of rejection.**

The instant claims are drawn to a method of stimulating production of a plurality of type I interferon (IFN) subtype, comprising contacting type I interferon producing cells (IPCs) with an amount of immunostimulatory nucleic acid effective to induce secretion of at least two type I interferons, wherein said immunostimulatory nucleic acid is at least 10 nucleotides long and comprises a poly-G sequence at each end and a central palindromic sequence comprising an unmethylated CpG dinucleotide, the same method wherein the IPCs are isolated or wherein the IPCs are precursor type 2 dendritic cells.

Claims 1-2 of the issued U.S. Patent No. 6,429,199 are directed to a method for activating a dendritic cell comprising contacting a dendritic cell with an isolated nucleic acid containing at least one unmethylated CpG dinucleotide wherein the nucleic acid is from about 8-80 bases in length in an amount effective to activate the dendritic cell, wherein the dendritic cell is an isolated dendritic cell or wherein the method is performed *ex vivo*. The issued U.S. Patent No. 6,429,199 specifically teaches that a dendritic cell includes immature dendritic cells, mature dendritic cells as well as precursor or progenitor dendritic cells (see col. 17, lines 9-12), and that unmethylated CpG containing nucleic acid sequences that are useful for stimulating dendritic cells include sequences shown in Table 1-7, including the 1585 ODN having the sequence 5'-ggGGTCAACGTTGACgggg-3' (col. 16, lines 20-41, Table 4). The issued U.S.

Patent No. 6,429,199 further teaches that oligonucleotide containing Gs at both ends showed increased stimulation, particularly if the oligodeoxyribonucleotide were rendered nuclease resistant by phosphorothioate modification of the terminal internucleotide linkage (col. 20, lines 53-66).

The issued U.S. Patent No. 6,429,199 does not specifically teach the use of dendritic cells that produce type I interferons or precursor type 2 dendritic cells.

However, at the effective filing date of the present application, Siegal et al. already teach that CD4+CD11c- type 2 dendritic cell precursors (pDC2s) are the principle type I interferon-producing cells in human blood, producing 200 to 1000 times more IFN than other blood cells after microbial challenge (see abstract). Siegal et al. further teach that pDC2s are an effector cell type of the immune system that is critical for antiviral and antitumor immune responses (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of the issued U.S. Patent No. 6,429,199 by specifically utilizing pDC2s in the methods of activating a dendritic cell in light of the teachings of Siegal et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification because Siegal et al. specifically teach that pDC2s are an effector cell type of the immune system that is critical for antiviral and antitumor immune responses (see abstract), and that the issued U.S. Patent No. 6,429,199 also teaches specifically the utilization of any precursor or progenitor dendritic cells (see col. 17, lines 9-12). It is further noted that the modified method is indistinguishable from that of the presently

claimed invention, and therefore the modified method also produces the same effects as recited by the instant claims.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of the issued U.S. Patent No. 6,429,199 and the teachings of Siegal et al. as well as a high level of skill of an ordinary skilled artisan in the art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

Claims 1-24, 65, 82 103, 202-263 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER